

REMARKS

A. The Status of the Claims and the Amendments

Claims 132-137, 142-145, 152-159, 161-163, 167, and 175-177 have been previously canceled without prejudice, as claims drawn to non-elected species. New claims 185-250 have been added. No new matter has been introduced in the newly added claims. Upon entry of the amendment, Claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, and 178-250 will be pending.

B. First Rejection Under 35 U.S.C. § 103(a)

Claims 116-131, 138-141, 146-151, 160, 164-166, 168-170, 173, 174, and 178-184 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,695,460 to Siegel et al. in view of U.S. Patent No. 5,648,098 to Porter (item 2, page 3 of the Office Action). This rejection is respectfully traversed on the following grounds.

To establish a *prima facie* case of obviousness, the three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference as proposed by the Examiner; (2) there must be a reasonable expectation of success and (3) the prior art reference must teach or suggest all of the claim limitations. MPEP § 2143. Applicant submits that at least two of the above criteria have not been met.

The Examiner has conceded (see, the end of third paragraph on page 5 of the Office Action), that Siegel et al. fail to describe a method which includes “applying to the patient ultrasonic energy having a frequency between about 750 kHz and 3 MHz,” as recited in claims 116 and 164. To cure this deficiency of Siegel et al. the Examiner proposes to combine the teachings of Siegel et al. and Porter, because Porter discloses that the ultrasound equipment capable of generating the signal within the range of

frequencies between 20 KHz to several megahertz can be used, which includes the range of frequencies recited in claims 116 and 164.

However, such combination of references does not satisfy the criteria required to establish a *prima facie* case of obviousness. First, the Examiner has not shown that there is there any suggestion or motivation to modify the Siegel et al. reference by importing the teachings of Porter. The Examiner has based his conclusion of combinability of Siegel et al. and Porter on the fact that Porter shows a possibility of using frequencies in the range claimed in claims 116 and 164 (see, page 6, lines 5-8 of the Office Action). The Applicant respectfully disagrees.

It has been well established that mere possibility of modification of a reference is not enough to show a *prima facie* case of obviousness. More is needed, specifically, it is required that the prior art suggest the desirability of modification. See, e.g., In re Browner, 77 F.3d 422, 425, 37USPQ2d 1663, 1666 (Fed. Cir. 1996). Thus, the burden is on the Examiner to demonstrate that Siegel et al. has suggested that the range of frequencies that it teaches has to be improved. It is submitted there is no such suggestion in Siegel et al. The Examiner has stated that "the ordinary artisan would have been motivated to optimize the frequency range" used in Siegel et al. (see page 6, lines 10-12 of the Office Action) and would have used the frequencies of Porter. This statement is not supported by evidence.

While it is certainly possible to optimize the frequencies disclosed by Siegel et al., there is nothing in Siegel et al. showing that such optimization was sought or desired. Siegel et al. does not state or imply that their results are insufficiently good in any way and that any modification is needed. The Examiner did not show any reason why an artisan would be dissatisfied with the teachings of Siegel et al. The only reason for optimization provided by the Examiner is that such optimization is possible (see page 6, lines 10-12 of the Office Action). Under the In re Browner case, this is not enough

motivation to modify the Siegel et al. reference by combining the teachings of Siegel et al. and Porter.

Second, it is submitted that there is no a reasonable expectation of success from combining Siegel et al. and Porter. Indeed, as previously discussed, Siegel et al. state that “it has been found that when ultrasound is applied at a lower, **rather than a higher frequency**, the effectiveness of the method is markedly enhanced” (see, Col. 5, lines 29-31) (emphasis added), and the “clot dissolution is significantly greater with lower frequencies, between about 25 and about 39 KHz, compared to higher frequencies” (see, Col. 7, lines 58-60).

Therefore, it is submitted that one skilled in the art would not be motivated to modify the teachings of Siegel et al. towards the increase in frequency to 750 KHz or higher, because the teachings of Siegel et al. suggest that such modification will lead to worse results. Thus, no success can be reasonably expected from combining Siegel et al. and Porter, and, accordingly, this basic criterion needed to establish a *prima facie* case of obviousness, has not been met.

In view of the foregoing it is submitted that each of claims 116 and 164 is patentably distinguishable over Siegel et al. in view of Porter. Each of claims 117-131, 138-141, 146-151 and 160 depends, directly or indirectly on claim 116 and is considered patentable for at least the same reason. Each of claims 165, 166, 168-174, and 178-184 depends, directly or indirectly on claim 164 and is considered patentable for at least the same reason. Reconsideration and withdrawal of the rejection of claims 116-131, 138-141, 146-151, 160, 164-166, 168-170, 173, 174. and 178-184 are respectfully requested.

C. Second Rejection Under 35 U.S.C. § 103(a)

Claims 116-120, 160, 164-166, 171-174, and 178-180 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,380,411 to Schlieff in view of the article by Holmes et al. (Journal of Urology, vol. 144, pp. 159-163 (1990)) (item 6, page 6 of the Office Action). This rejection is respectfully traversed on the following grounds.

The basic criteria that must be met to establish a *prima facie* case of obviousness are as described above. Applicant submits that these criteria have not been met. Indeed, Schlieff describes various methods for destroying tumor cells using microbubbles and ultrasound, but fails to teach that a biologically active agent is used or that the frequency of the ultrasound is between 750 kHz and 3 MHz, as required by claims 116 and 164. In addition, Schlieff describes his methods only with respect to *in vitro* applications, but fails to teach *any in vivo* applications and thus does not describe the step of administering a composition to a patient. Holmes et al. fail to provide the description lacking in Schlieff.

Indeed, Holmes et al. teach using high energy shock waves for destroying prostate cancer tissues. Holmes et al. also utilizing chemotherapeutic agents in conjunction with the application of the shock waves. However, there is nothing in Holmes et al. teaching the use of ultrasound having between 750 kHz and 3 MHz. All that is disclosed is that the shock waves are generated by lithotripsy using a XL-1 experimental machine; and the operating frequency that was used was just one shock per second.

It is clear that the successful treatment in Holmes is correlated to the number of shock waves, but there is nothing more that one skilled in the art can learn from Holmes et al. for the purposes of the present application. The expression "high energy shock waves" is relative and it would be speculation to guess what frequencies were meant. For example, if one followed the teachings of Siegel et al., ultrasound at a frequency of just 100 kHz would be a source of energy that could be considered "high," yet such frequency is well below the range recited in claims 116 and 164.

Accordingly, it is submitted that even if the teachings of Shlief and Holmes et al. are combined as suggested by the Examiner, the combination would still fail to disclose or suggest every limitation of claims 116 and 164.

In view of the foregoing it is submitted that each of claims 116 and 164 is patentably distinguishable over Shlief in view of Holmes et al. Each of claims 117-120, and 160 depends, directly or indirectly on claim 116 and is considered patentable for at least the same reason. Each of claims 165, 166, 171-174, and 178-180 depends, directly or indirectly on claim 164 and are considered patentable for at least the same reason. Reconsideration and withdrawal of the rejection of claims 116-120, 160, 164-166, 171-174, and 178-180 are respectfully requested.

D. New Claims

New claims 185-225 include independent claims 185, 210 and 226. Claims 185 and 210 recite a biologically active agent that is "a genetic material, a peptide, a beta-agonist, an anti-asthmatic, a steroid, a cholinergic agent, an anti-cholinergic agent, a 5-lipoxygenase inhibitor, a leukotriene inhibitor, an anti-neoplastic agent, an antibiotic, an anti-tumor drug, a radiation sensitizer, an anti-histamine, an anti-coagulant, an anti-inflammatory, a hormone, a growth factor, an angiogenic factor and a mitotic inhibitor."

Siegel et al. and Porter only describe thrombolytic agents and neither describe nor suggest using any other agents. Siegel et al. specifically teach that their invention is directed "to introduction of a microbubble media that does not contain an active agent." Accordingly, claims 185-225 are considered patentable over Siegel et al. in view of Porter. Furthermore, claims 185-225 are considered patentable over Shlief in view of Holmes et al. for the reason discussed above.

With respect to claims 226-250, they are directed to a combination of original claims 121, 123, 124, 126, and 128, as per the suggestion made by the Examiner's during

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the interview on August 2, 2005. Applicant gratefully acknowledges the Examiner's advice.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

No fee is deemed to be due in connection with this response. However, if any fee is due, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,

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